Wnt Inhibition Correlates with Human Embryonic Stem Cell Cardiomyogenesis: A Structure-Activity Relationship Study Based on Inhibitors for the Wnt Response.

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Public Summary:
Human embryonic stem cell-based high-content screening of 550 known signal transduction modulators showed that one "lead" (1, a recently described inhibitor of the proteolytic degradation of Axin) stimulated cardiomyogenesis. Because Axin controls canonical Wnt signaling, we conducted an investigation to determine whether the cardiogenic activity of 1 is Wnt-dependent, and we developed a structure-activity relationship to optimize the cardiogenic properties of 1. We prepared analogues with a range of potencies (low nanomolar to inactive) for Wnt/beta-catenin inhibition and for cardiogenic induction. Both functional activities correlated positively ($r(2) = 0.72$). The optimal compounds induced cardiogenesis 1.5-fold greater than 1 at 30-fold lower concentrations. In contrast, no correlation was observed for cardiogenesis and modulation of transforming growth factor beta (TGFbeta)/Smad signaling that prominently influences cardiogenesis. Taken together, these data show that Wnt signaling inhibition is essential for cardiogenic activity and that the pathway can be targeted for the design of druglike cardiogenic molecules.

Scientific Abstract:
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